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1. Your reference

RL/LAS/P07294GB

2. Patent application number
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9620934.1

- 8 OCT 1996

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Molecular Drives Limited

2 The Square
University of Glasgow
Glasgow G12 8QQ

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

GB

4. Title of the invention

Multi-Well Containers

5. Name of your agent *(if you have one)*

Cruikshank & Fairweather

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

19 Royal Exchange Square
Glasgow G1 3AE
United Kingdom

Patents ADP number *(if you know it)*

547002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

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Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

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See note (d))

YES

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Continuation sheets of this form	
Description	13
Claim(s)	
Abstract	no
Drawing(s)	2

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Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature Cruikshank & Fairweather Date 07.10.96

CRUIKSHANK & FAIRWEATHER

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr Robert Lind - Tel: 0141 221 5767

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MULTI-WELL CONTAINERS

The present invention relates to multi-well containers and in particular to multi-well containers arranged to receive and hold a precisely defined volume of liquid for the purpose of conducting chemical or biochemical assays.

Multi-well trays or plates comprising an array of extremely small wells are commonly used in medicine and science to facilitate testing of a liquid analyte. One particular area of use is blood screening where blood or blood products are introduced into the wells to test for conditions such as HIV, hepatitis etc.

Tests typically involve an antigen-antibody reaction, where the surfaces of the wells are coated with an antigen which is selected to bind to an antibody for which the blood is to be tested. The wells are then filled with the blood or blood product and, if the antibody is present in the blood or blood product, it will bind to the antigen in the wells. Typically, the well is then rinsed clean and a further reactant which binds either to exposed antigens or antibodies, introduced into the wells in order to enable identification of the wells which contain antibody. This further reactant may produce a colour change or some other observable change.

It is often necessary to fill each well of a multi-well tray with a precisely defined volume of analyte. This is normally achieved using a single or multi-headed micro-pipette. However, this process is often time consuming

and, particularly where a large number of wells are to be filled, can lead to a number of wells being missed.

In certain circumstances it is necessary that the wells of a tray be contained within a substantially closed container, e.g. to avoid the risk of contamination of the wells and of leakage of contaminated material. With trays such as this, it may be difficult or impossible to gain access to the wells to enable them to be filled with a micro-pipette.

It is an object of the present invention to overcome or at least mitigate the disadvantages of known multi-well trays.

According to a first aspect of the present invention there is provided a multi-well container comprising upper and lower closely spaced opposed surfaces defining a space therebetween, the lower surface having a plurality of wells provided therein and there being provided at least two spaced apart openings into said space, wherein a liquid can be introduced into said space through one of said openings to substantially fill the space and the wells and can be subsequently withdrawn through the same or the other opening to empty said space, leaving only the wells filled with liquid.

The volume of liquid introduced into each well when using the container of the present invention is substantially defined by the volume of the well. The accuracy and precision with which the wells can be filled is therefore defined by the accuracy and precision with

which the wells can be fabricated and which is generally high. Furthermore, because a multiplicity of wells can be filled by way of a single injection and withdrawal of liquid through an opening into the space containing the wells, the wells can be filled extremely rapidly.

The container of the present invention provides for the filling of a plurality of wells in a substantially closed container, the only openings into that container being the liquid injection opening and a second 'vent' opening.

The container of the present invention simplifies the process of cleaning or rinsing previously filled wells as this can be achieved by repeatedly injecting and withdrawing liquid through one of said openings.

Preferably, the spacing between said upper and lower surfaces is sufficiently small to facilitate the flow of liquid in said space by capillary (or capillary like) action. Typically, the spacing will be less than 1mm and preferably less than 0.5mm.

Preferably, said upper and lower surfaces are substantially planer.

The wells may have any suitable geometry. For example, the wells may be provided in said lower surface by dimples. Alternatively, the wells may have substantially straight sidewalls, e.g. so that the sidewalls extend substantially vertically in use. Vertical sidewalls assist in preventing the transfer of liquid between adjacent wells.

The surfaces may be provided by respective plates which are spaced apart by one or more spacer walls.

Preferably, the opening through which liquid is introduced into said space is provided through either the upper or lower surface and, more preferably, through the upper surface. The additional opening may be provided through said upper or lower surface or through a side surface.

Preferably, said opening for introducing a liquid comprises a relatively small opening arranged to receive the end of a syringe or similar liquid injecting device, where the opening forms a substantially air tight seal around said end.

Preferably, said lower surface of the container is treated to increase the hydrophilicity of the surface. This helps to prevent the formation of air pockets in the container and aids filling of the wells. The treatment may comprise for example exposing the surface to a wetting agent, e.g. poly-l-lysine, or exposing the surface to a gas plasma.

In one embodiment of the present invention, the multi-well container is in the form of a disc. The disc effectively comprises upper and lower circular plates, the internal surfaces of which respectively define said upper and lower opposed surfaces. Preferably, said opening for introducing liquid into the space comprises a hole passing through the upper circular plate. Preferably, the second opening is provided at the peripheral edge of the disc.

The space between the upper and lower plates may be subdivided to provide a plurality of multi-well containers by one or more dividing walls, in which case each space is provided with an opening and a vent to enable each space to be independently filled. The dividing walls may extend radially and/or may be concentric to one another.

Preferably, at least one of the upper and lower plates forming the container are transparent to enable optical inspection of the wells from outside the container. The other of the upper and lower plates may comprise a reflecting surface so that radiation entering into the container through the transparent plate transverses the container in both direction, resulting in an increased signal to noise ratio for the optical inspection.

In an alterative embodiment of the present invention there is provided a disc arranged to receive a plurality of inserts each of which comprises a generally planar upper surface having a plurality of wells provided therein. For each insert, the disc comprises a substantially planar surface arranged in use to oppose said substantially planar insert surface, means for retaining the insert so that the respective planar surfaces are in closely spaced opposition to one another, and said at least two openings.

Preferably, the opening for filling the container is provided through the planar surface of the disc. The vent opening is preferably provided adjacent to the peripheral edge of the disc.

The disc preferably comprises upper and lower circular

plates separated by radially extending spacers. The spacers define slots between the plates for receiving said inserts. Preferably, said planar surface of each insert comprises upstanding walls around at least a portion of its periphery for the purpose of sealing the inner edges of the insert to the opposed planar surface of the disc, thereby to prevent seepage of liquid around the insert.

According to a second aspect of the present invention there is provided a method of filling the wells of the container of the above first aspect of the present invention and comprising introducing a liquid into said space through one of said openings to substantially fill the space and the wells and subsequently withdrawing the liquid from the space through the same or the other opening to leave only the wells filled with liquid.

Preferably, the method comprises forming an air tight seal between the liquid introducing opening and an end region of a syringe or similar liquid injecting device and injecting liquid through the opening into the space and subsequently sucking liquid out of the space through the opening.

According to a third aspect of the present invention there is provided a container for use in conducting optical assays of a liquid analyte, the container comprising:

a disc for rotation about a central axis, the disc having a plate and a plurality of substantially radially extending walls projecting from the lower surface of the plate, wherein said walls sub-divide the disc into a

plurality of disc segments; and

a plurality of disc inserts arranged to be received by respective disc segments and to be retained therein by interengagement with said radially extending walls,

the container further comprising for each disc segment an opening through the plate for introducing a liquid analyte into the space between the plate and the disc insert.

Preferably, the disc further comprises a lower plate, spaced apart from said upper plate by said radially extending walls. More preferably, both said plates are circular.

Preferably, the upper surface of each disc insert and the opposed surface of the plate are substantially planar, and more preferably are in closely spaced opposition.

Preferably, a vent opening is provided for each disc segment around the periphery thereof, between the radially outer edge of the upper plate and each disc insert.

For a better understanding of the present invention and in order to show how the same may be carried into effect reference will now be made, by way of example, to the accompanying drawings, in which:

Figure 1 shows a multi-well container according to a first embodiment of the present invention;

Figures 2a to 2c illustrate three steps involved in filling the wells of the container of Figure 1;

Figure 3 shows a multi-well container according to a second embodiment of the present invention.

Figure 4 shows a disc-style container for conducting multi-tests.

There is shown in Figure 1 a multi-well container having a box-like construction with a rectangular cross-section. The container comprises an upper plate 2, a lower plate 3, and side and rear spacers 4, 5, 6, all of which are made of a transparent plastics material. The front of the container, indicated generally by the reference numeral 7, is open to the surrounding space.

The spacers 4, 5, 6 are dimensioned to produce a uniform spacing d between the opposed inner surfaces of the upper and lower plates 2, 3. Spacing d is chosen such that liquid is able to flow through the space between the upper and lower plates in a controlled manner (possibly by capillary action). Generally, d is less than 0.5mm.

A small opening 8 extends through the centre of the upper plate 2 to communicate the inner space with the space surrounding the container. This opening 8 is located close to the rear wall 6 in order to prevent air-locks forming in the container during filing (see below).

A regularly spaced array of wells or dimples are formed in the upper surface of the lower plate 3. Typically, the container is constructed of a plastics material and the wells are produced by suitably moulding the lower plate 3 or by etching or pressing. The wells typically have a volume of 5μl and any suitable number of wells may be provided.

Figures 2a to 2c illustrate the process by which the

wells 9 of the container are filled with a liquid analyte. The end of a syringe 10 containing the liquid analyte 11 is pressed into the opening 8 provided in the upper plate 2 of the container 1 (Figure 2a) so as to form an air-tight seal between the periphery of the syringe and the inner surface of the opening. The plunger of the syringe 10 is then depressed to force the liquid through the opening 8 into the space within the container 1. Due to the capillary flow of liquid through the space, the entire space, including the wells 9, is filled, before liquid begins to flow through the front open face 7 of the container 1. When it is observed that all of the wells are covered with liquid, and preferably prior to liquid flowing out through the front face 7 (Figure 2b), the plunger of the syringe 10 is withdrawn. This action empties the space of liquid, leaving only the wells 9 filled with liquid (Figure 2c). As with the filling process, liquid flows from the space in a controlled manner. No puddles or drops of liquid remain in the space, other than in the wells 9.

It will be appreciated that prior to introducing the liquid analyte into the container, for example during the manufacture of the container, the wells 9 of the container may be coated with an appropriate reactant. For example, if it is desired to conduct antigen-antibody reactions, the wells 9 may be coated with an antigen. Once the wells 9 have been filed with the analyte, any antibodies present in the liquid analyte will bind with the antigens contained in the wells. If it is necessary to conduct a further

reaction in the wells, e.g. to bind a coloured or fluorescent label to the bound antibodies or exposed antigens, it is possible to repeat the steps of Figures 2a to 2c in order to introduce the labelled components into the wells 9. Prior to introducing the labelled components, if it is necessary to rinse the wells and the inner surfaces of the container 1, this is again easily achieved by repeating steps 2a to 2c with the syringe containing, for example, distilled water.

There is illustrated in Figure 3 a second embodiment of the present invention which is in the form of a disc 12 designed for use with a rotating scanning device having a CD player type format. One such device is described for example in WO96/09548. The disc 12 shown in Figure 3 comprises a pair of upper and lower circular plates 13, 14 sandwiched together to provide a cylindrical space 15 therebetween. This space is divided into eight compartments 16 by radially extending spacers 17. A plurality of wells (not shown) are provided in each compartment 16 by suitably forming the upper surface of the lower circular plate 14 and as described with reference to Figure 1.

Each compartment 16 provides a container which can be filed independently via an opening 18 provided through the top surface of the compartment 16. The peripheral edge 19 of each compartment is open to the surrounding space to provide a vent for the compartment 16.

In order to enable the disc 12 to be compatible with

scanning devices such as are described in WO96/09548, the upper and/or lower plates 13, 14 are of a transparent material to enable a light beam to be scanned across the wells. Additionally, the disc 12 is provided with a hole 20 through its centre in order to enable the disc to be supported on a rotatable shaft.

As is described in WO96/09548, one of the surfaces of the upper or lower plates 13, 14 may be provided with digitally encoded address information which can be read by the scanned light beam. This information may be encoded by way of "pits" and "lans" pressed or moulded into one of the plates. This address information can be used to provide accurate information on the region of the disc which is begin scanned by the light beam.

It will be appreciated that modifications may be made to the above described embodiments without departing from the scope of the present invention. For example, the opening through which the liquid analyte is introduced may be provided through the lower plate of the multi-well container. This opening may be arranged to receive the tip of a syringe needle. The vent opening may also be provided in any one of the walls of the container although it is preferably provided in a peripheral wall.

There is shown in Figure 4 a disc-style container 21 which comprises upper and lower circular plates 22, 23 which are spaced apart by a number of radially extending spacer walls 24 to create a plurality of disc segments 25. The inner surfaces of the circular plates 22, 23 are both

planar.

Each disc segment 25 is arranged to receive a disc insert 26a, 26b which comprises a generally triangularly shaped (in cross-section) insert plate of plastics material. An upwardly extending wall 27 is provided around the upper periphery of the insert, except for around the radially outermost peripheral edge. The combined thickness of the insert plate and the peripheral wall 27 is marginally less than the spacing provided between the upper and lower plates 22, 23 of the disc 21 so that the insert can be pressed fitted into one of the disc segments 25 to provide a container space between the upper surface of the insert plate and the lower surface of the upper disc plate 22. An opening 28 is provided through the upper plate 22 into each disc segment whilst the space between the radially outermost peripheral edge of the insert plate and the upper plate 22 provides a further opening into the disc segment.

The surface of the insert plate is provided with a plurality of wells 29 as described with respect to Figure 1. These can be filled by introducing liquid into the disc segment through the upper opening 28 and subsequently withdrawing the liquid through the same opening.

In a modification to the embodiment of Figure 4, the wells are absent from the upper surface of the plate and that plate retains its planar surface to enable a thin, uniform layer of liquid to be introduced into the space between the upper disc plate and the insert plate. A

reagent or reagents (e.g. an antigen) may be applied directly to the planar surface of the insert plate by for example applying spots of reagent thereto.

For certain applications, it may be appropriate to provide each insert with a lid which can be slid into the space between the insert and the upper plate 22 of the disc following filling of the wells. The lower surface of the lid may be arranged to be flush with the surface of the insert so as to close off each well. This prevents liquid from being thrown out of the wells during spinning of the disc.

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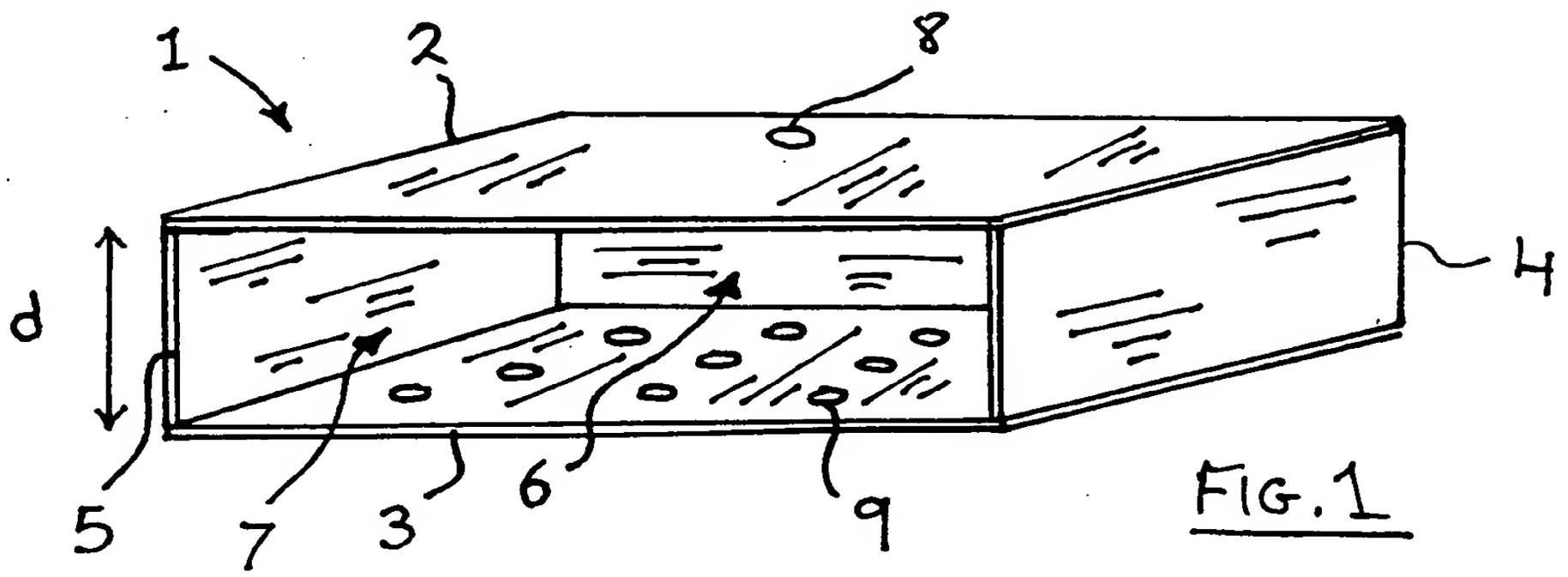

FIG. 1

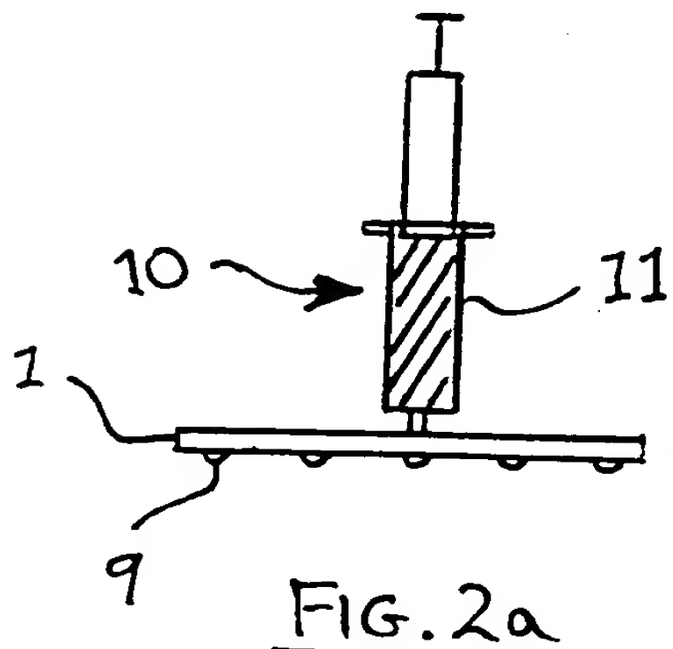

FIG. 2a

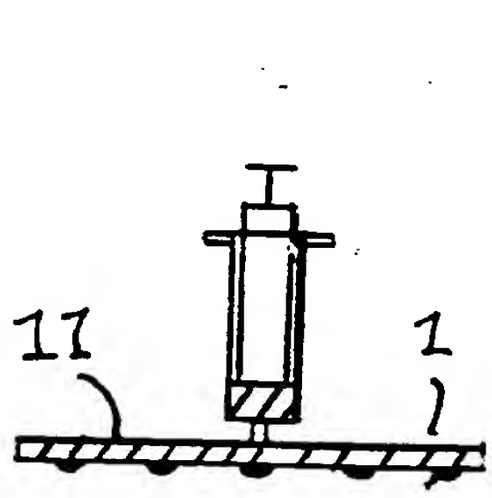

FIG. 2b

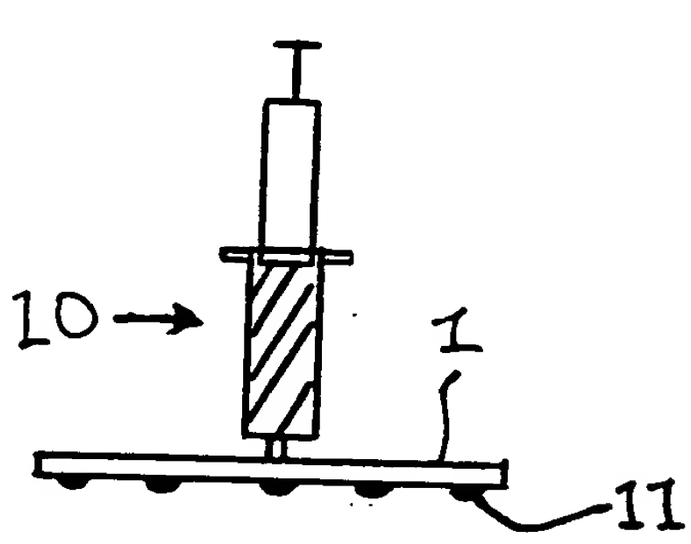

FIG. 2c

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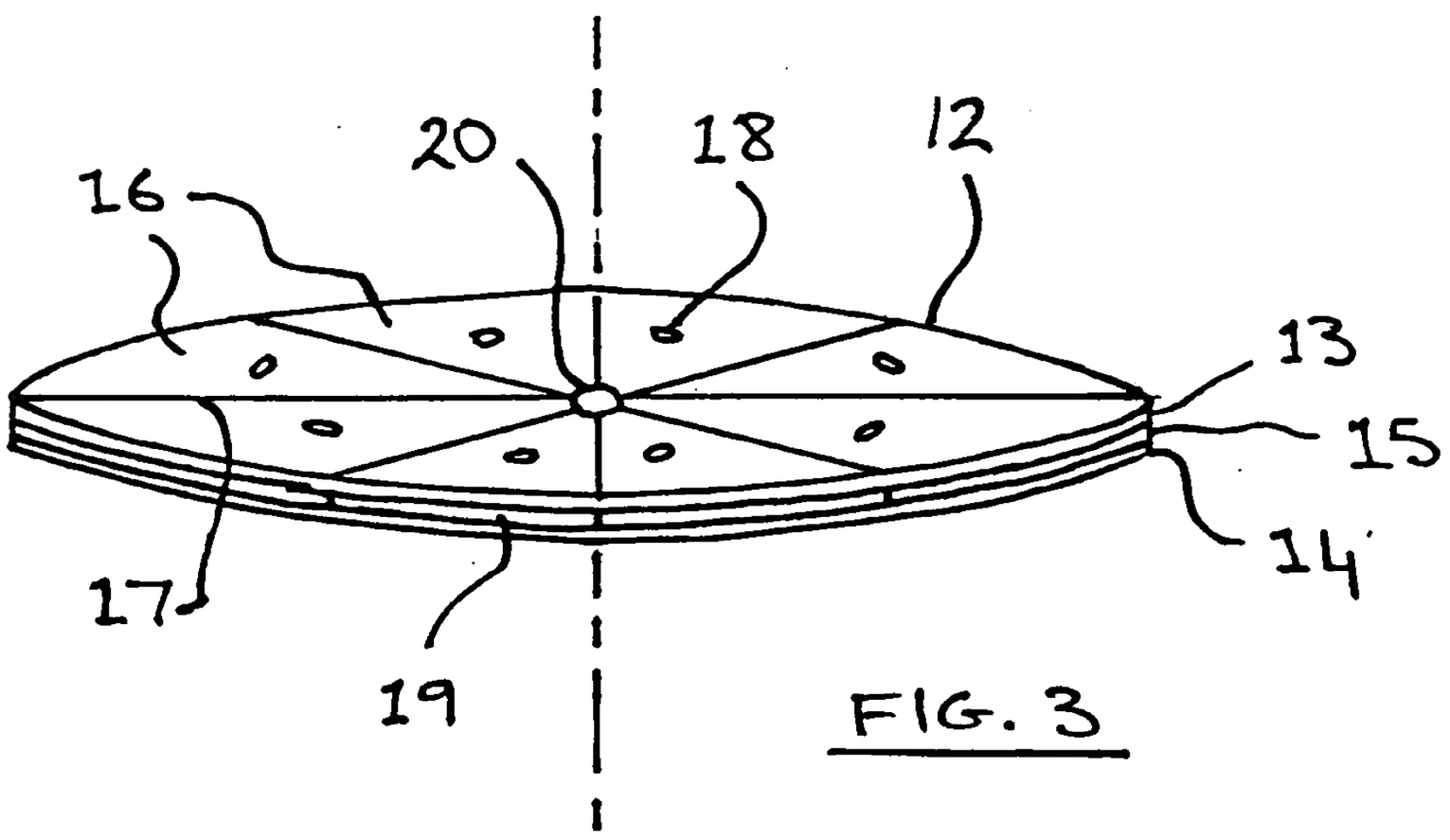

FIG. 3

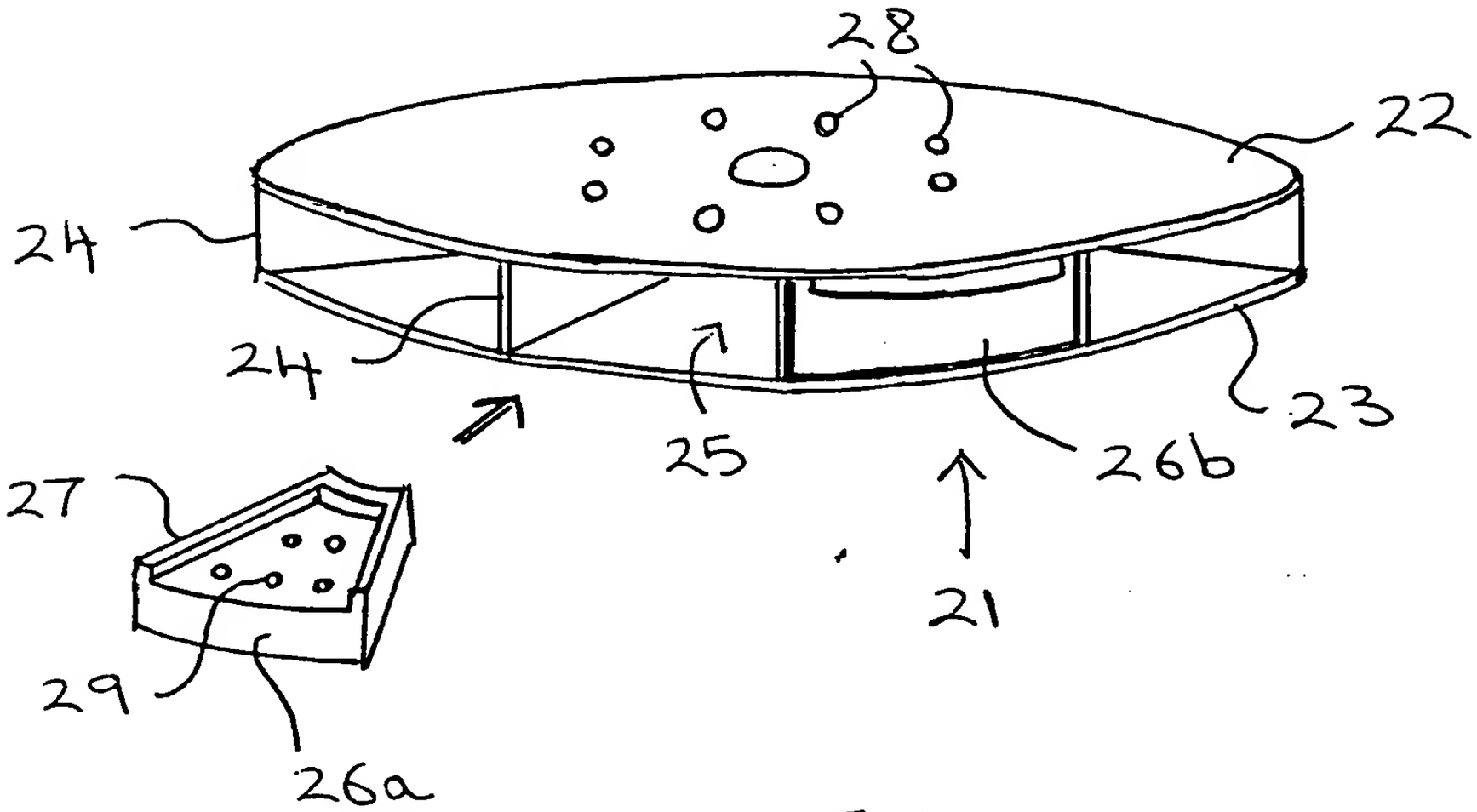

FIG. 4

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